Remarks/Arguments

Reconsideration of the above-identified application in view of the present amendment is respectfully requested.

By the present amendment, claims 64 and 77 have been cancelled. Claim 59 has been amended to recite that the BER inhibitor comprises an AP endonuclease inhibitor and the AP endonuclease inhibitor includes a small molecule compound having a primary amine group that binds to an aldehyde group of the AP site and prevents AP endonuclease-mediated cleavage of phosphodiester bonds. Support for the limitation that the AP endonuclease inhibitor is a small molecule compound can be found on pages 18-21, 36-38, and 53-54. Support for the limitation that the compound is a primary amine that binds to an aldehyde group of an AP site can be found on page 53. Claims 65 and 78 have been amended to correct the dependency of the respective claims. Claim 234 was added and recites that the method further includes administering a PARP inhibitor. Support for this limitation can be found on page 8, paragraph 4, and Fig. 7. Claim 235 was added and further recites that the AP endonuclease inhibitor is selected from various aminooxy compounds identified on pages 18-21. Claims 236-241 were further added. Support for the limitations of these claims can be found in the preceding claims.

Below is a discussion of the 35 U.S.C. §112, first paragraph, written description rejection of claims 59, 60, 75, and 98, the 35 U.S.C. §112, first paragraph, enablement rejection of claims 59, 60, 65, 75, 78, and 98, and the 35 U.S.C. §103(a) rejection of claims 59, 60, 65, 75, 77, and 98.

1. 35 U.S.C. §112, first paragraph, written description rejection of claims 59, 60, 64, 75, 77 and 98

Claims 59, 60, 75, and 98 stand rejected under 35 U.S.C. §112, first paragraph, as containing subject matter, which is not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention, specifically rejecting the term "AP endonuclease inhibitors".

As discussed above, claim 59 has been amended to recited that that the AP endonuclease inhibitor is a small molecule compound that has a primary amine group and binds to an aldehyde group on the an AP site to prevent AP endonuclease-mediated cleavage of phosphodiester bonds.

Applicants respectfully traverse this rejection as applied to the amended claims because (1) the specification of the application clearly allows persons of ordinary skill in the art to recognize that Applicants were in possession of "AP endonuclease inhibitors" as recited in claims 59, 60, 75, and 98, and (2) the Office Action has failed to establish a prima facie case that the specification does not satisfy the written description requirement.

A written description of a genus of compositions to be used in a method can be achieved by (i) a description of a representative number of compositions falling within the genus, or (ii) a recitation of distinguishing structural features common to members of the genus, which features constitute a substantial portion of the genus. *See e.g., Eli Lilly,* 119 F.3d at 1568 ("A written description of an invention involving a chemical genus, like a description of a chemical species, 'requires a precise definition, such as by structure, formula, [or] chemical name,' of the claimed subject

matter sufficient to distinguish it from other materials."). Although the statute does not require representative species, "where no explicit description of a generic invention is to be found in the specification... mention of representative compounds may provide an implicit description upon which to base generic claim language." *Robins,* 429 F.2d at 456-57. In other words, representative species "are a means by which certain requirements of the statute may be satisfied." *Id.*

A representative number of species can be described by a "disclosure of sufficiently detailed, relevant identifying characteristics," such as "complete or partial structure, other physical and/or chemical properties, *functional characteristics when coupled with a known or disclosed correlation between function and structure,* or some combination of such characteristics." *Enzo Biochem, Inc.* v. *Gen-Probe Inc.,* 323 F.3d 956, 964 (Fed. Cir. 2002). Thus, an additional way to describe a genus can be (iii) reliance on a known or disclosed correlation between function and structure. *See e.g., Amgen, Inc.* v. *Hoechst Marion Roussel, Inc.,* 314 F.3d 1313, 1332 (Fed. Cir. 2003) ("the requirement may be satisfied if in the knowledge of the art the disclosed function is sufficiently correlated to a particular, known structure").

The specification of the present application describes AP endonuclease inhibitors by specific examples, formulas, and functional characteristics such that one skilled in the art would recognize that Applicants had possession of the claimed invention.

> Page 18, lines 18+ notes that AP endonuclease inhibitors include:
>
> "Methoxyamine (MX), N-ethylmaleimide, O^6-benzylguanine, and compounds having structures of formula I: wherein X is O or NH, Y is O, S, or NH, Z is absent or represents O, S, or NH, and R represents a

> hydrogen or a hydrocarbon moiety, and pharmaceutically acceptable salts thereof."

Page 18, lines 29+ further describes the structure and functional characteristics of other compounds and AP endonuclease inhibitors.

> "In single-nucleotide BER, the deoxyribose phosphate (dRP) in the abasic site is removed by the lyase activity of DNA pol β. Compounds such as methoxyamine react with the aldehyde of an abasic site, making it refractory to the β-elimination step of the dRP lyase mechanism, thus blocking single-nucleotide BER."

In other words, small molecule compounds, such as methoxyamine, that include a primary amine group can react with an aldehyde group to form an imine or Schiff base reaction product and this imine or Schiff base reaction product is refractory to the β-elimination step of the dRP lyase mechanism, thus blocking single-nucleotide BER.

Page 19, lines 1+ further notes other compounds, all of which include primary amine groups, can react with the aldehyde groups of the AP sites:

> "Suitable AP endonuclease inhibitors may act by binding to AP sites and preventing APE-mediated cleavage of phosphodiester bonds, or by acting directly on AP endonuclease. Other compounds that may possess AP endonuclease inhibitory activity (e.g., by binding to AP sites and preventing APE-mediated cleavage of phosphodiester bonds) include Other potential inhibitors include O-benzylohydroxylamine; ethyl aminooxyacetate; aminooxyacetic acid; ethyl aminooxyacetate; $H_2NOCHMeCO_2H$; carboxymethoxyamine; aminooxyacetic acid; $HN{=}C(NH_2)SCH_2CH_2ONH_2$; $H_2NO(CH_2)_3SC(NH_2){=}NH$; $MeOC(O)CH(NH_2)CH_2ONH_2$;$H_2NOCH_2CH(NH_2)CO_2H$; canaline; $H_2NO(CH_2)_4ONH_2$; O-(p-nitrobenzyl)hydroxylamine; 2-amino-4-(aminooxymethyl)thiazole; 4-(aminooxymethyl)thiazole; O,O'-(o-phenylenedimethylene)dihydroxylamine; 2,4-dinitrophenoxyamine; O,O'-(m-phenylenedimethylene)dihydroxylamine; O,O'-(p-phenylenedimethylene)dihydroxylamine; $H_2C{=}CHCH_2ONH_2$; $H_2NO(CH_2)_4ONH_2$; $H_3C{-}{-}(CH_2)_{15}{-}{-}O{-}{-}NH_2$, 2,2'-(1,2-ethanediyl)bis(3-

> aminooxy)butenedioic acid dimethyl diethyl ester; compounds having any of the following structures: and pharmaceutically acceptable salts of any of these compounds."

Moreover, the specification describes functional characteristics of the small molecule compounds coupled with a disclosed correlation between function and structure that defines the genus of the compounds. Claim 59 recites that the AP endonuclease inhibitors are small molecule compounds that are primary amines, which bind to an aldehyde group on the AP site to prevent AP endonuclease-mediated cleavage of phosphodiester bonds. The specification notes on pages 17+ that:

> "Injury to DNA is minimized by enzymes that recognize errors, remove them, and replace the damaged DNA with corrected nucleotides. DNA damage occurs when a single-strand break is introduced, a base is removed leaving its former partner unpaired, a base is covalently modified, a base is converted into another that is not appropriately paired with the partner base, or a covalent link is introduced between bases on opposite strands. Excision repair systems remove the mispaired or damaged base from the DNA strand and then synthesize new DNA to replace it. Base excision repair (BER) is initiated during replication of DNA and allows for correction of damaged bases/mispaired bases prior to completion of replication.
>
> Base excision repair is initiated by a DNA glycosylase that removes N-glycosidic (base-sugar) bonds, liberating the damaged base and generating an abasic site (AP site). An apurinic or apyrimidinic site results from the loss of a purine or pyrimidine residue, respectively, from DNA. uracil residues result from the spontaneous deamination of cytosine and can lead to a CT transition if unrepaired. There is also a glycosylase that recognizes and excises hypoxanthine, the deamination product of adenine. Other glycosylases remove alkylated bases (such as 3-methyladenine, 3-methylguanine, and 7-methylguanine), ring-opened purines, oxidatively damaged bases, and in some organisms, UV photodimers.
>
> The AP site is further processed by a 5'-3' endonuclease (AP endonuclease (APE)) that incises the phosphodiester bond on both sides of the damaged purine or pyrimidine base. The AP

> endonucleases introduce chain breaks by cleaving the phosphodiester bonds at the AP sites."

As discussed above, the specification further notes on pages 18-19 that:

> "Compounds such as methoxyamine react with the aldehyde of an abasic site, making it refractory to the beta-elimination step of the dRP lyase mechanism, thus blocking single-nucleotide BER. Suitable AP endonuclease inhibitors may act by binding to AP sites and preventing APE-mediated cleavage of phosphodiester bonds, or by acting directly on AP endonuclease. Other compounds that may possess AP endonuclease inhibitory activity (e.g., by binding to AP sites and preventing APE-mediated cleavage of phosphodiester bonds)…"

Additionally, the specification discloses a method of identifying additional AP endonuclease inhibitors for use in the present invention. The specification describes a high throughput screening assay to identify new inhibitors of BER which have the ability to block AP site cleavage.

Page 37, line 31 to page 39, line 71 (and Fig. 23A and 23B) state:

> "High-throughput screening methods include two molecular reaction assays:
> 1. Analysis of chemical--modified AP Sites assayed by Aldehyde Reactive Probe (ARP). This is a competitive assay to measure the reactivity with AP site between ARP reagent (Dojindo Molecular Technologies Inc., Gaithersburg, Md.) and the screening compounds. ARP and MX have a similar reactivity with AP sites. They react specifically with an aldehyde group that is open ring form of the AP sites. Thus this assay will allow identification of compounds with potential to block AP site repair based on the binding affinity and efficiency to AP sites of screening compounds compared to ARP and MX.
> a. AP site standard preparation: AP sites were produced in a calf thymus DNA by heat/acid-buffer solution. Intact calf thymus DNA was added to sodium citrate buffer (10 mM sodium citrate containing 10 mM $NaH._2PO_4$ and 10 mM NaCl, pH 5.0) and held at 70 °C. for 30 min. The reaction was stopped by chilling rapidly on ice, and the DNA was then precipitated with cold ethanol, washed with 70% ethanol, dried, and resuspended in sterilized distilled water.
> b. AP-DNA (15 pg) was incubated with test compounds at different concentrations at 37 °C. for 30 min prior to ARP (1 mM) or ARP alone

(Dojindo Molecular Technologies Inc., Gaithersburg, Md.) for 30 min. After precipitation and wash with ethanol, DNA was resuspended in TE buffer (10 mM Tris-HCl, 1 mM EDTA, pH 7.2). DNA was heat-denatured at 100.degree. C. for 5 min, quickly chilled on ice, and mixed with an equal amount of 2 M ammonium acetate. The single-stranded DNA was then immobilized on a BAS-85 NC membrane (Schleicher and Schuell) using a vacuum filter device (Schleicher and Schuell). The NC membrane was incubated with streptavidinconjugated horseradish peroxidase (BioGenix) at room temperature for 30 min. After NC membrane was rinsed with washing buffer containing NaCl (0.26 M), EDTA (1 mM), Tris-HCl (20 mM), and Tween 20 (1%), ARP-AP sites are visualized with ECL reagents (Amersham Corp.) (FIG. 22A) and quantitated by scanning densitometer (FIG. 22B).

2. AP sites cleavaged by AP-endonuclease (APE). This assay confirms that AP sites modified by potential BER inhibitors are resistant to cleavage by APE, (Trevigen, Gaithersburg, Md.) a BER protein. The assay may be performed as follows (see also FIGS. 23A and B):

a. AP site is prepared by replacing single nucleoside with deoxyuridine in duplex oligonucleotides (40 mer).

b. Regular AP site is produced in the duplex oligonucleotides by human uracil DNA glycosylase (LIDGase, Trevigen, Gaithersburg, Md.) to remove the uracil residue.

c. To generate MX-adducted AP site substrates: the UDG-treated duplex oligonucleotides are mixed with 10 mM MX in buffer containing 10 mM KPO4, pH 7.1 and incubated at 37 ℃. After 30 min, the substrates are recovered by ethanol precipitation, lyophilized, resuspended in water, and stored at -20 ℃.

d. APE-cleavage reaction: DNA substrates containing either regular AP-sites or chemicalmodified AP sites are incubated with APE (Trevigen, Gaithersburg, Md.) for 30 min and reactants are precipitated with 100% cold ethanol, washed with 70% ethanol and resuspended in TE buffer. The reactants are resolved by denaturing 20% polyacrylamide gel electrophoresis and visualized by silver staining (Silver Staining Kit, Pharmacia Biotech)."

Additionally, Example 14 of the application describes an assay in which additional AP endonuclease inhibitors are identified by a simple competitive assay that measures the binding affinity of other primary amine compounds to the aldehyde group of an AP site compared to an aldehyde reactive probe.

Example 14 states:

> "The results that methoxyamine (MX) potentiated the cytotoxic effect of temozolomide (TMZ) and BCNU indicated that molecules targeting abasic lesions in DNA are important approach to improve chemotherapeutic efficacy of alkylating agents. On the basis of a similar molecular reaction to MX, (e.g., a primary amine with the carbonyl group of the abasic site), we tested whether a compound (Compound A) would have the ability to bind to AP site generated by TMZ and enhance the killing effect of TMZ. A has a MX-like structure to bind to AP site and also has fluorescence molecules to provide a signal for direct detection of modified AP sites using cellular image. We found that this compound was able to bind to AP sites assayed with aldehyde-reactive probe (ARP) that competitively binds to the aldehyde group of AP site. A-modified AP sites were refractory to cleavage of APE, suggesting that it can block base excision repair (BER) pathway by inhibiting repair of AP sites. Cellular image showed 30% of cells with fluorescent signal that was located in nuclear at 2 hr after treatments with TMZ plus A. In contrast, cells treated with A alone had no visualized fluorescence signal. This data suggest that A specifically binds to AP sites in DNA. In in vitro study, we observed A at non-toxic concentrations (1 mM) sensitized cells to TMZ-cytotoxicity 2-3-fold. In a xenograft model, A (2 mg/kg) combined with TMZ (80 mg/kg) enhanced anti-tumor effect in HCT116 and DLD1, two xenograft tumors with very high resistance to TMZ. Tumor growth delays were 13 days in HCT116 and 12 days in DLD1 treated with the combination of A and TMZ over TMZ alone. Thus, A has a similar effect to MX on interruption of BER and can potentiate chemotherapeutic agents such as alkylating agents. Results are depicted in FIGS. 14-16."

Thus, not only does the specification disclose specific AP endonuclease inhibitors that are small molecule compounds on pages 18+, distinguishing characteristics to identify the AP endonuclease inhibitor, that is small molecule compounds that are primary amines and bind to the aldehyde group of an AP site, and an assay to identify new AP endonuclease inhibitors of BER, the specification identifies a specific functional characteristic of potential BER inhibitors (blocking AP site cleavage by forming Schiff-bases with the aldehyde group of the AP site).

The Federal Circuit has stated that the written description requirement does not require the applicant "to describe exactly the subject matter claimed, [instead] the description must clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." *In re Gosteli*, 872 F.2d 1008, 1012, 10 U.S.P.Q.2D (BNA) 1614, 1618 (Fed. Cir. 1989) (citations omitted). The disclosure of a class compounds as well as distinguishing identifying characteristics is sufficient to show that the Applicants were in possession of the claimed invention. See, e.g., *Pfaff v. Wells Elecs., Inc.*, 525 U.S. 55, 68, 119 S.Ct. 304, 312, 48 USPQ2d 1641, 1647 (1998); *Eli Lilly*, 119 F.3d at 1568, 43 USPQ2d at 1406; *Amgen, Inc. v. Chugai Pharmaceutical*, 927 F.2d 1200, 1206, 18 USPQ2d 1016, 1021 (Fed. Cir. 1991). As a general principle, when the compounds encompass a broad genus or when there is substantial variation within the genus, the written description requirement will not likely be satisfied by disclosing only a single species within the genus. *Carnegie Mellon, 541 F.3d at 1124-25.* However, a patent specification need not describe every detail of every embodiment. *Vas-Cath,* 935 *F.2d at 1563.* Examples are not required, and "[a] claim will not be invalidated on *section 112* grounds simply because the embodiments of the specification do not contain examples explicitly covering the full scope of the claim language." *LizardTech. Inc. v. Earth Res. Mapping, PTY, Inc.,* 424 *F.3d 1336, 1345 (Fed. Cir. 2005).* An actual reduction to practice [*26] is also unnecessary to satisfy the written description requirement. *Falkner,* 448 *F.3d al 1364 n.8; Rochester. 358 F.3d at* 926 ("Constructive reduction to practice is an established method of disclosure".

The specification of the present application clearly allows one skilled in the art to recognize what is claimed based on the disclosure of the characteristics of AP endonuclease inhibitors, the disclosure of a vast number of AP endonuclease inhibitors, as well as means to identify additional AP endonuclease inhibitors. Therefore, in view of the foregoing, Applicants have conveyed with reasonable clarity to those skilled in the art that, as of the filing date sought, that they were in possession of the invention, and that the invention, in that context, is claimed.

Additionally, regardless of the sufficiency of the disclosure in the specification, the Office Action has failed to establish a prima facie case that the specification does not satisfy the written description requirement. The inquiry into whether the description requirement is met must be determined on a case-by-case basis and is a question of fact. *In re Wertheim*, 541 F.2d 257, 262, 191 USPQ 90, 96 (CCPA 1976). A description as filed is presumed to be adequate, unless or until sufficient evidence or reasoning to the contrary has been presented by the examiner to rebut the presumption. See, e.g., *In re Marzocchi*, 439 F.2d 220, 224, 169 USPQ 367, 370 (CCPA 1971). The Examiner, therefore, must have a reasonable basis to challenge the adequacy of the written description. The Examiner has the initial burden of presenting by a preponderance of evidence why a person skilled in the art would not recognize in an applicant's disclosure a description of the invention defined by the claims. *Wertheim*, 541 F.2d at 263, 191 USPQ at 97.

The Office Action has failed to provide any evidence in fact or reasoning that the specification fails to meet the written description requirement. The Office Action

has merely cited a Federal Circuit decision without correlating the decision with the specific disclosure in the present application.

The Office Action cites Univ. of Rochester v. G.D. Searle, 69 USPQ2d 1886, 1892 (CAFC 2004) stating:

> "that the ability to find compounds based on a functional property, even when the method of determining the same is clearly disclosed , does not meet the written description requirement."

In *Rochester,* a disputed patent claimed all compounds that could inhibit the cox-2 enzyme without inhibiting the cox-1 enzyme. According to the Rochester court, it was inappropriate for the patentee to make this claim when it had not identified these compounds structurally but, rather, had only suggested as assay that might be used to identify the compounds.

In the present application, Applicants have provided more than to just suggest an assay, which might be used to identify useful compounds. As discussed above, the Application describes a specific AP endonuclease inhibitor for use in the present invention (*e.g.,* methoxyamine), the general structure of compounds useful as AP endonuclease inhibitors in the present invention, a specific functional characteristic of potential BER inhibitors (blocking AP site cleavage), and an assay to identify new BER inhibitors.

Since the specification adequately discloses a combination of identifying characteristics that distinguish the claimed invention from other materials, it would lead one of skill in the art to the conclusion that Applicants were in possession of the claimed species.

Moreover, the Office Action has provided no evidence to doubt veracity of the statements made in the specification or to show in any manner that the subject matter recited in the application and claims is unpredictable. It is well established that a general allegation of "unpredictability in the art" is not a sufficient reason to support a rejection for lack of adequate written description. MPEP 2163.04.

Accordingly, Applicants respectfully request that the 112 first paragraph written description rejection of claims 59, 60, 75, and 98 be withdrawn because the specification of the application clearly allows persons of ordinary skill in the art to recognize Applicants were in possession of "AP endonuclease inhibitors" as recited in claim 59, 60, 75, and 98, and the Office Action failed to established a prima facie case that the specification does not satisfy the written description requirement.

2. 35 U.S.C. §112, first paragraph, enablement rejection of claims 59, 60, 64, 65, 75, 77, 78, and 98

Claims 59, 60, 65, 75, 78, and 98 stands rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling a method of potentiating a therapeutic effect of temozolamide by combination with methoxyamine (MX), does not reasonably provide enablement for treating the broader method of potentiating a therapeutic effect of anticancer agents which induce formation of AP sites by combination with base excision repair inhibitors.

The Office Action argues that to practice the present invention as claimed in the current application, a person of ordinary skill in the art would have to engage in undue experimentation. The Office Action specifically argues that the specification does not reasonably provide enablement for treating the broader method of

potentiating a therapeutic effect of anticancer agents, which induce formation of AP sites.

Applicants traverse the foregoing rejection as applied to the currently amended claims and submit that the amount of direction or guidance disclosed in the specification is sufficient to enable the skilled artisan to make and use the claimed methods using only routine experimentation.

"[T]o be enabling, the specification ... must teach those skilled in the art how to make and use *the full scope of the claimed invention* without 'undue experimentation.'" *In re Wright*, 999 F.2d 1557, 1562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993) at 1561 (emphasis added), *quoted in Genentech, Inc. V. Novo Nordisk A/S*, 108 F.3d 1361, 1365 (Fed. Cir. 1997). Thus, "there must be sufficient disclosure, either through illustrative examples or terminology, to teach those of ordinary skill how to make and use the invention as broadly as it is claimed." *In re Vaeck*, 947 F.2d 488, 496 & n. 23 (Fed. Cir. 1991), *quoted in Enzo Biochem, Inc. V. Calgene, Inc.*, 188 F.3d 1362, 1374 (Fed. Cir. 1999). Some experimentation, even a considerable amount, is not "undue" if, e.g., it is merely routine, or if the specification provides a reasonable amount of guidance as to the direction in which the experimentation should proceed. *See In re Wands*, 858 F.2d 731, 737 (Fed. Cir. 1988).

Facts should be considered in determining, whether a specification is enabling include: (1) the quantity of experimentation necessary to practice the invention, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the

relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims. *In re Wands,* 858 F.2d 731, 737 (Fed. Cir. 1988).

Claim 59 recites a method for potentiating a therapeutic effect of an anticancer agent that induces formation of AP sites in cancer cells of a patient. The method includes administering to a patient with cancer an anticancer agent that induces formation of AP sites in cancer cells of the patient and an amount of a base excision repair (BER) inhibitor that is effective to potentiate the cytotoxicity of the anticancer agent to the cancer cells. The BER inhibitor comprises an AP endonuclease inhibitor that includes a small molecule compound having a primary amine group that binds to an aldehyde group of the AP site and prevents AP endonuclease-mediated cleavage of phosphodiester bonds.

With respect to amended claim 59, Applicants have disclosed in the instant specification known anticancer agents and the use of such agents to induce formation of AP sites as recited in claim 59. Specifically, the specification recites at page 22, lines 19+, that:

> "Anticancer agents that induce the formation of AP sites include intercalating agents such as bleomycin, adriamycin, quinacrine, echinomycin (a quinoxaline antibiotic), and anthrapyrazoles.
>
> Radiation, such as gamma radiation, UVA, and UVB, can be used to generate AP sites according to the methods of the invention. Ultraviolet light is absorbed in DNA with the formation of UV-specific di-pyrimidine photoproducts. Exposure to gamma irradiation, UVA, and UVB can induce damaged pyrimidine photodimers.
>
> Anticancer agents that induce the formation of AP sites include DNA oxidizing agents such as hydrogen peroxide.
>
> Anticancer agents that induce the formation of AP sites include alkylating agents such as temozolomide (TMZ), 1,3-bis(2-chloroethyl)-

1-nitrosourea (BCNU), $MeOSO_2(CH_2)_2$-lexitropsin (Me-Lex), cis-diamminedichloroplatinum II (cisplat; cis-DDP), mitomycin bioreductive alkylating agents, quinones, streptozotocin, cyclophosphamide, nitrogen mustard family members such as chloroambucil, pentostatin (and related purine analogs), fludarabine, bendamustine hydrochloride, chloroethylating nitrosoureas (e.g., lomustine, fotemustine, cystemustine), dacarbazine (DTIC), and procarbazine. In certain embodiments, the alkylating agent is a nitrosoruea such as a mustine, i.e., a compound having a structure of Formula II, wherein R is an optionally substituted hydrocarbon substituent, such as an alkyl, cycloalkyl, heterocyclyl, aryl, heteroaryl, cycloalkylalkyl, heterocyclylalkyl, aralkyl, or a heteroaralkyl: In preferred embodiments, R is a substituent shown below or to the right of Formula I, i.e., the chemotherapeutic is carmustine (BCNU), chlorozotocin, fotemustine, lomustine, nimustine, ranimustine, or semustine. In certain related embodiments, the chloroethyl group of Formula I is replaced by a methyl group, as in streptozocin. In certain embodiments, however, R is not 2-chloroethyl, i.e., the compound is not BCNU.

Alkylating agents can function by adding methyl groups to DNA, cross-linking macromolecules essential for cell division, and linking guanine bases in DNA through their N_7 atoms. Both inter- and intra-strand cross-links can be mediated by alkylating agents. Inter-strand cross-links prevent the separation of the DNA strands necessary for cell division, and by being more difficult to repair, constitute the more lethal lesion.

In certain embodiments, the anticancer agent is selected from radiosensitizers such as 5-iodo-2'-deoxyuridine (IUdR), 5-fluorouracil (5-FU), 6-thioguanine, hypoxanthine, uracil, ecteinascidin-743, and camptothecin and analogs thereof.

In certain embodiments, the anticancer agent is not temozolomide. In certain embodiments, the anticancer agent is not BCNU. In certain embodiments, the anticancer agent is not PE128723, 6-AN, 3-AB, BCNU, or temozolomide."

These known anticancer agents can be used to treat various cancers. The specific cancers treated by each of these anticancer agents are well known to one skilled in the art. For example, Williams and Lemke, *Foye's Principals of Medicinal Chemistry.*, 5th ed. Baltimore: Lippincott, Williams, & Wilkins, 2002, 928-945 indicate, which cancers these anticancer agent are currently used or approved for

treating. Other sources, such as the Nation Cancer Institute, as well as the FDA indicate specific cancers that these anticancer agents can be used for treating.

Applicants have discovered that these anticancer agents (as well as other anticancer agents) can function at least in part by forming AP sites of DNA of the specific cancer cells the agents are administered to treat. Specifically, the present application states at page 17 that:

> "Injury to DNA is minimized by enzymes that recognize errors, remove them, and replace the damaged DNA with corrected nucleotides. DNA damage occurs when a single-strand break is introduced, a base is removed leaving its former partner unpaired, a base is covalently modified, a base is converted into another that is not appropriately paired with the partner base, or a covalent link is introduced between bases on opposite strands. Excision repair systems remove the mispaired or damaged base from the DNA strand and then synthesize new DNA to replace it. Base excision repair (BER) is initiated during replication of DNA and allows for correction of damaged bases/mispaired bases prior to completion of replication.
>
> Base excision repair is initiated by a DNA glycosylase that removes N-glycosidic (base-sugar) bonds, liberating the damaged base and generating an abasic site (AP site). An apurinic or apyrimidinic site results from the loss of a purine or pyrimidine residue, respectively, from DNA. uracil residues result from the spontaneous deamination of cytosine and can lead to a C-T transition if unrepaired. There is also a glycosylase that recognizes and excises hypoxanthine, the deamination product of adenine. Other glycosylases remove alkylated bases (such as 3-methyladenine, 3-methylguanine, and 7-methylguanine), ring-opened purines, oxidatively damaged bases, and in some organisms, UV photodimers.
>
> The AP site is further processed by a 5'-3' endonuclease (AP endonuclease (APE)) that incises the phosphodiester bond on both sides of the damaged purine or pyrimidine base. The AP endonucleases introduce chain breaks by cleaving the phosphodiester bonds at the AP sites."

The present application also teaches that the BER inhibitors can potentiate the effect of these cancer agents by inhibiting base excision repair, which is one of

the mechanisms the cancer cells use to inhibit the cytotoxic function of the anticancer agents.

Applicants have also provided working examples in the present application to show that BER inhibitors can be used to potentiate the effect of anticancer agents that form AP sites. Specifically, Example 1 of the present application shows that methoxyamine, a BER inhibitor, potentiates the effect of TMZ, an anticancer agent that induces formation of AP sites; Example 4 shows that BER inhibitors potentiate the effect of chlorethylating agents that induce formation of AP sites; Example 10 shows that BER inhibitors potentiate the effect of an oxidizing agent that induces formation of AP sites in cancer cells; and Example 11 shows that BER inhibitors potentiate the effect of radiosensitizing agents.

Thus, the appropriate question for determining whether the enablement requirement has been satisfied in the present case is whether the instant specification teaches the ordinary skilled artisan a method of administering to a patient with cancer an anticancer agent that induces formation of AP sites in cancer cells of the patient and an amount of an AP endonuclease inhibitor that is effective to potentiate the cytotoxicity of the anticancer agent to the cancer cells. Applicants respectfully submit that one skilled in the art would have been able to perform the foregoing methods based on the specification as well as the examples noted in the specification.

Additionally, the Office Action provides no evidence to doubt the veracity of the objective statements made in the specification. It is well established that "[t]he Examiner has the initial burden of establishing a reasonable basis to question the

enablement provided for the claimed invention" *In re Wright*, 999 F.2d 1557, 1562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993). A requirement for some experiment does not prevent the satisfaction of the enablement requirement. *Northern Telecom, Inc. v. Datapoint Corp.*, 15 USPQ2d 1321, 1329 (Fed. Cir. 1990). The Federal Circuit has made it clear that "[w]hen rejecting a claim under the enablement requirement of section 112, the PTO bears an initial burden of setting forth a reasonable explanation as to why it believes that the scope of protection provided by that claim is not adequately enabled by the description of the invention provided in the specification of the application; this includes, of course, *providing sufficient reasons for doubting any assertions* in the specification as to the scope of enablement." *In re Wright*, 999 F.2d 1557, 1562, 27 USPQ2d 1510, 1561-1562 (Fed. Cir. 1993). (Emphasis added).

Specifically, the Examiner has not provided any factual evidence to doubt the objective truth of the Applicants' statements, which must be relied upon for enabling support; namely, that AP endonuclease inhibitors can be administered in combination with an anticancer agent that forms AP sites in cancer cells to potentiate the cytoxicity of the anticancer agents.

The Examiner in the current Office Action merely states;

> "while one of ordinary skill may know what cancers may be treated by known anti-cancer agents, the instant claims are not limited to the treatment by their know respective anticancer agents, but instead the claims are directed to administering anticancer agents which induce formation of AP sites, generally, to treat cancers, generally. Thus, one of ordinary skill would be subject to undue experimentation when determining what cancers may be treated by the anticancer agents, given the increased potency of the combination."

Applicants fail to see the relevance of this argument. "Title 35 does not require that a patent disclosure enable one of ordinary skill in the art to make and use a perfected, commercially viable embodiment absent a claim limitation to that effect." *CFMT, Inc. v. Yieldup Int'l Corp.,* 349 F.3d 1333, 1338 (Fed. Cir. 2003). *See also In re Cortright,* 165 F.3d 1353, 1359 (Fed. Cir. 1999) (claims to method of "restoring hair growth" encompassed achieving full head of hair, but did not require it).

Claim 59 is directed to a method for potentiating a therapeutic effect of an anticancer agent that induces formation of AP sites in cancer cells of a patient by administering an amount of an AP endonuclease inhibitor that is effective to potentiate the cytotoxicity of the anticancer agent to the cancer cells. It is true that the specification contemplates using anticancer agent that induces formation of AP sites in cancers, but practicing the claimed method does not require a skilled artisan to treat specific cancers with anticancer agents that are not known to induce formation of AP sites in the cancers. As discussed on page 37 of the specification of the application,

> "Recent evidence indicates that AP sites are common DNA lesions for anticancer drugs that attack DNA, generating modified bases that are removed by DNA glycosylases. Thus, BER inhibitors have the potential to improve the therapeutic efficacy of a broad spectrum of anticancer agents."

Moreover, as discussed in Example 14 of the specification of the present application, the ability of an anticancer agent to create AP sites in specific cancers can be readily determined using an aldehyde reactive probe. Thus, a skilled artisan can rely on well known anticancer agents that are known to generate AP sites to

practice the method of the invention as well as identify specific anticancer agents that generate AP sites in specific cell lines.

The Examiner's apparent position that the specification cannot teach how to use the claimed method unless it teaches solutions to all the problems in the field of cancer therapy is contrary to controlling case law. *See, e.g., In re Brana,* 51 F.3d 1560, 1568 (Fed. Cir. 1995).

In B*rana,* the claims were directed to compounds disclosed as anticancer agents. *Id.* at 1562. The USPTO rejected the claims as nonenabled, *id.* at 1563-64, despite working examples in Brana's specification showing treatment of cancer in a mouse model. *Id.* at 1562-63. The USPTO argued that the results of the mouse testing "are not reasonably predictive of the success of the claimed compounds for treating cancer in humans." *Id.* At 1567. The court concluded that this position "confuses the requirements under the law for obtaining a patent with the requirements for obtaining government approval to market a particular drug for human consumption." *Id.* The *Brana* court held that "[u]sefulness in patent law, and in particular in the context of pharmaceutical inventions, necessarily includes the expectation of further research and development. The stage at which an invention in this field becomes useful is well before it is ready to be administered to humans." *Id* at 1568.

Here, the claims are simply directed to a method of potentiating the therapeutic effect of an anticancer agent that induces formation of AP sites in cancer cells of a patient by administering an AP endonuclease inhibitor to the cells of the subject, and Applicants' specification provides a working example demonstrating just

that in mice. The Examiner has discounted the specification's working examples because "one of ordinary skill would be subject to undue experimentation when determining what cancers may be treated by the anticancer agents, given the increased potency of the combination". However, enablement - especially in the context of pharmaceutical inventions - includes an expectation of further research and development. Thus, enablement is not precluded even if the claims encompass methods, that have not yet overcome all the obstacles to their clinical use.

Accordingly, for the reasons of record and in contrast to the Examiner's assertions, the instant specification does enable one skilled in the art to practice the claimed invention and it would not require undue experimentation to practice the invention as claimed. Moreover, the reference relied upon by the Examiner provides no evidence that the claimed invention could not be successfully practiced. Applicants therefore, requests reconsideration and withdrawal of the 35 U.S.C. §112, first paragraph, rejection of claim 59.

Claims 60, 65, 75, 78, and 98 depend either directly or indirectly from claim 59, therefore Applicants respectfully request that the 35 U.S.C. §112, first paragraph, rejection of claims 60, 65, 75, 78, and 98 also be withdrawn.

3. 35 U.S.C. §103(a) rejection of claims 59, 60, 64, 65, 75, 77, and 98

Claims 59, 60, 64, 65, 75, 77, and 98 are rejected under 35 U.S.C. §103(a) as being unpatentable over Fortini et al. (Carcinogenesis vol. 13 no. 1 (1992) pp. 87-93).

Claim 59 is not obvious in view of Fortini et al. because: (I) Fortini et al. do not teach administration of an anticancer agent and an AP endonuclease inhibitor to a

cancer cell of a patient; and (II) one of ordinary skill in art would not find it predictable and/or have a reasonable expectation of success in view of Fortini et al. that an AP endonuclease inhibitor could potentiate the cytoxic effect of an anticancer agent that induces formation of an AP sites in a cancer cell of a patient.

The question of obviousness is resolved on the basis of underlying factual determinations including: (1) the scope and content of the prior art; (2) the level of ordinary skill in the art; (3) the differences between the claimed invention and the prior art; and (4) secondary considerations of nonobviousness, if any. *Graham v. John Deere Co.*, 383 U.S. 1, 17 (1966). While the analysis under 35 U.S.C. § 103 allows flexibility in determining whether a claimed invention would have been obvious, *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 418 (2007), it still requires showing that "there was an apparent reason to combine the known elements in the fashion claimed by the patent at issue." *Id.* "We must still be careful not to allow hindsight reconstruction of references to reach the claimed invention without any explanation as to how or why the references would be combined to produce the claimed invention." *Innogenetics, N.V. v. Abbott Labs.*, 512 F.3d 1363, 1374 n.3 (Fed. Cir. 2008).

In *KSR*, the Supreme Court stated that when an obvious modification "leads to the anticipated success," the invention is likely the product of ordinary skill and is obvious under 35 U*.S.C.* § *103,* 127 S. *Ct. at 1742.* "[O]bviousness cannot be avoided simply by a showing of some degree of unpredictability in the art so long as there was a reasonable probability of success." *Pfizer, 480 F.3d at 1364* (citing *In re Corkill,* 771 *F2d 1496, 1500 (Fed. Cir. 1*985)).

Cases following *KSR,* however, have found that obviousness is not found where the prior art [gives] either no indication of which parameters [are] critical or no direction as to which of many possible choices is likely to be successful" *In re O'Farrell, 853 F.2d* 894, *903 (Fed. Cir*. 1988). In such cases, "courts should not succumb to hindsight claims of obviousness. "*In re Kubin,* 561 *F.3d 1351, 1359 (Fed Cir. 2009).* Similarly, patents are not barred just because it was obvious "to explore a new technology or general approach that seemed to be a promising field of experimentation, where the prior art gave only general guidance as to the particular form of the claimed invention or how to achieve it." *In re O'Farrell, 853 F.2d at 903.*

Fortini et al. teach administration of methoxyamine in combination with an alkylating agent to CHO cells in vitro. Fortini et al. note on page 87, paragraph 2 that they

> "show in this paper that MX [methoxyamine], by reacting with these AP sites, protects CHO from cytoxicity, mutagenicity and sister chromatid exchanges (SCE) induced by Sn1 type ethylating agents. Furthermore, this protective effect is also extended to methylating agent damage."

As discussed in the Office Action, Fortini et al. also note for CHO cells, which are administered an Sn2 alkylating agent:

> "the 3 h exposure to MX significantly potentiated the cytoxicity of 30 exposures to DES (Figure 4, bottom) or MMS (data not shown). A 3 h exposure did not affect the cloning efficiency of CHO cells." (Page 89, column 2, lines 7-10).

Thus, Fortini et al. teach that in CHO cell lines methoxyamine provides protective effect to Sn1 type alkylating agents but can potentiate the cytotoxicity of Sn2 type alkylating agents.

Fortini et al., however, do not teach administration of an anticancer agent and an AP endonuclease inhibitor to a cancer cell and/or that an AP endonuclease inhibitor can potentiate the cytoxic effects of an anticancer agent administered to a cancer cell of a patient. As discussed in Applicants previous response, a CHO cell is not a cancer cell of a patient with cancer. Additionally, the Office Action does not provide any evidence in fact or technical literature to show that an *in vitro* CHO assay is recognized by the skilled artisan as being a model for a cancer cell or of treating cancer in vivo and/or the that one of ordinary skill in the art would find it predictable and/or have a routine expectation of success that methoxyamine could potentiate the cytoxic effect of an Sn1 or Sn2 alkylating agent administered to a cancer cell of a patient.

Moreover, at the time of filing the application, one of ordinary skill in art would have not found it predictable and/or had a reasonable expectation of success that methoxyamine could be used to potentiate the cytoxicity of Sn1 or Sn2 alkylating agent administered to a cancer cell in a patient. At time of filing the present application, as discussed in U.S. Patent No. 4,325,950, which was previously noted by the Examiner, the use of BER inhibitors in combination with anticancer agents for the treatment of cancer in a patient was unpredictable. The '950 application states in column 1, lines 22+ that:

> "Caffeine is an inhibitor of DNA repair and it is has been shown in cell culture studies that caffeine greatly increases cell kill caused by cis $Pt(NH_3)_2Cl_2$. While these cell cultures studies have been demonstratably successful in vitro, they have not been successfully replicated in vivo, i.e., no enhancement of anti-cancer activity occurs when these compounds are combined."

Moreover, Wyatt et al. note in Chem. Res. Toxicol. 2006 19(12):1580-94 note that:

> "Despite recent progress, the complexity of DNA damage responses to methylating agents is still being discovered. In particular, there is growing understanding of pathways such as homologous recombination, lesion bypass, and mismatch repair that react when the response of direct reversal proteins and BER is insufficient. Furthermore, the importance of proper balance within the steps in BER has been uncovered with the knowledge that DNA structural intermediates during BER are deleterious. A number of issues complicate elucidating the downstream responses when direct reversal is insufficient or BER is imbalanced. These include inter-species differences, cell-type specific differences within mammals and between cancer cell lines, and the type of methyl damage or BER intermediate encountered." (Abstract)

Accordingly, one skilled in the art would recognized that BER response can differ in different species and different cell types due to the differences of DNA damage responses in each cell type. This was noted in the specification of the present application in Example 13 where Applicants observed no potentiation of TMZ toxicity with addition of methoxyamine to either CD34+ cells or murine bone marrow progenitors. From these results, Applicants hypothesized that,

> "AP sites formed during repair of TMZ-induced N7 mG and N3 mA adducts would also be recognized by Topo I and Topo II. However since Base Excision Repair [BER] is normally quite efficient, we further hypothesized that the impact of Topo I and Topo II would be most important after MX inhibition of BER; increased unrepaired MX adducted AP sites should increase Topo mediated strand breaks and apoptosis. Therefore, potentiation of TMZ cytotoxicity by MX would be dependent on Topo I and II. We found that levels of topoisomerases I and II were much higher (>20-fold) in human tumor cell lines than in either human CD34+ or murine bone marrow progenitor cells. Thus, we propose that MX does not potentiate TMZ toxicity in hematopoietic progenitors because these cells express low levels of Topo I and II. Lack of Topo I and II results in less cleavable complex formation, fewer double strand DNA breaks, and less apoptosis."

Thus, the prior art indicates that different cells lines have different DNA damage responses and that AP endonuclease inhibitors may potentially have a protective effect when combined with least some anticancer agents (*e.g.,* Sn1 type agents in CHO cell lines) and/or fail to potentiate cytotoxic effect of at least some anticancer agents in other cell lines (*e.g.,* CD34+ and bone marrow progenitor). Moreover, the Office Action has failed to provide any evidence showing one skilled in the art would find it predictable and/or had a reasonable expectation of success that the effects of methoxyamine and an Sn2 type alkylating agent on a CHO cell are predictive of the effects of methoxyamine and an Sn2 type alkylating agent on a cancer cell let alone a cancer cell in a patient.

It has been held that a claim is not obvious where the improvement of the prior art is more than a predictable use of prior art elements according to their known function or use. *In re Kubin,* 561 F.3d 1351, 1359 (Fed Cir. 2009). Accordingly, a method for potentiating a therapeutic effect of an anticancer agent that induces formation of AP sites in cancer cells of a patient by administering to a patient with cancer an anticancer agent that induces formation of AP sites in cancer cells of the patient and an amount of a base excision repair (BER) inhibitor that is effective to potentiate the cytotoxicity of the anticancer agent to the cancer cells was unpredictable at the time of the invention and one skilled in the art would not have had a reasonable expectation of success in view of the known art and especially the teachings of Fortini et al. Therefore, one skilled in the art would not find claim 59 obvious in view of Fortini et al.

Claims 60, 65, 75, 78, and 98 depend either directly or indirectly from claim 59 and are therefore allowable over Fortini et al. because of the aforementioned deficiencies discussed above with respect to the rejection of claim 59 and because of the limitations recited in claims 60, 65, 75, 78, and 98.

In view of the foregoing, it is respectfully submitted that the above-identified application is in condition for allowance, and allowance of the above-identified application is respectfully requested.

Please charge any deficiency or credit any overpayment in the fees for this amendment to our Deposit Account No. 20-0090.

Respectfully submitted,

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